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neo-Clerodane Diterpenoids from *Scutellaria galericulata*

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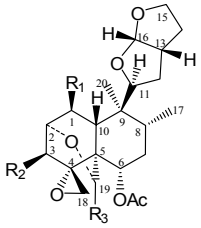
Four *neo*-clerodane diterpenoids, neoajugapyrin A, scutegalerins A and B and scutecolumnin C have been isolated from the acetone extract of the aerial parts of *Scutellaria galericulata*. Neoajugapyrin A and scutecolumnin C are reported in this species for the first time, whereas scutegalerins A and B are new compounds. NMR data of neoajugapyrin A are discussed in detail to support the proposed revised structure of ajugapyrin A.

Keywords: *Scutellaria galericulata*, *Ajuga pyramidalis*, Labiatae, *neo*-Clerodane diterpenes.

Scutellaria (Labiatae) species provide a rich source of *neo*-clerodane diterpenes [1] with potent insect antifeedant and antifungal activities [2,3]. Plant material of *S. galericulata* L. growing in the UK (Royal Botanic Gardens, Kew), Spain (Madrid province) and Bulgaria has been studied previously, and seven novel *neo*-clerodanes were reported: jodrellin T, 14,15-dihydrojodrellin T, galericulin [4], scutegalin A, scutegalin B [5], scutegalin C and scutegalin D [6], whereas jodrellin B was isolated previously from *S. woronowii* Juz. [2]. 14,15-Dihydrojodrellin T, scutegalin A, and scutegalin D were present in the Bulgarian plant [7]. All compounds, except galericulin, displayed a 2α,19-hemiacetal functionality. In continuation of our systematic studies on *Scutellaria* species [8-10], we have reinvestigated *S. galericulata* from a different geographical area. Here we report on the isolation of neoajugapyrin A (**1**), scutegalerin A (**2**), scutegalerin B (**3**) and scutecolumnin C (**4**), with full structural elucidation of **1** and **2**. Neoajugapyrin A (which turned out to be 3β-hydroxyscutecyprin) was isolated previously and named ajugapyrin A, but reported as 1β-hydroxyscutecyprin from *Ajuga pyramidalis* [11]. The previously proposed structure has now been found to be wrong and the name neoajugapyrin A is proposed to indicate the new revised structure (with improved NMR data). The trivial name scutegalerin A is given to the real, now isolated, 1β-hydroxyscutecyprin.

Two TLC homogeneous fractions and a mixture were obtained after chromatography of the acetone extract of the aerial parts of the Bulgarian plant. Compound **1** was isolated from the most polar fraction and the IR spectrum revealed the presence of hydroxyl and acetyl groups and, in addition, bands for (*E*)-2-methyl-2-butenoyl ester, but the absence of those for either a lactone or furan moiety. The ^{1}H NMR spectrum of **1** (250 MHz) was identical (direct comparison) with that previously reported for ajugapyrin A [11]. Owing to the limited NMR data available we completed a comprehensive NMR study (600 MHz) to improve the structural elucidation and facilitate identification in subsequent isolations. The ^{1}H-broadband-decoupled ^{13}C NMR and the DEPT spectra of **1** (Table 1) displayed 27 and 21 (5x CH_3, 6x CH_2, 10x CH) signals, respectively. Data of hexahydrofurofuran, tiglyl and acetyl moieties, as well as for C-6 to C-10 in ring B, were in close agreement with those for the scutecyprin parent system [12; Bozov and Penchev, unpublished data]. Some signal assignments and *J* constants are corrected owing to improved resolution of the ^{1}H NMR spectrum. Thus, spectral data of the tiglic acid moiety were in agreement with published values [5,12,13], but the clear multiplicities now observed for Me-4′ and Me-5′ pointed out the interchange of assignment of these signals (as appearing in [11]). Furthermore, the 4.40 *m* was reported as collapsing "into a *t* after addition of D_2O" pointing out a likely reversal of 1α/2β assignments. Moreover, since the δ_H 2.55 brd assigned to H-3α in scutecyprin [12] was not present, O-substitution at C-3 rather than at C-1 was considered a likely possibility requiring an unambiguous rational. Furthermore, the two O functions at C-2 and C-3 may be accounted for in two different ways depending on the carbon involved in the bridge to C-19 and the one with the free hydroxyl function, forming either the common 2.2.2 or a 3.2.1 bi-cyclic system. Detailed analysis of the HSQC/HMBC spectra for C-1 to C-5 established the C(2)-O-C(19) bridge unambiguously: δ_H 3.98 as H-2 [HMBC correlations with C-19, C-10 and the reciprocal H-19 to C-2], whereas H-3α (δ_H 4.40/δ_C 70.1) displayed only the reciprocal H-18 to C-3 correlation. The spin system in ring A (H-10—[H-1α–H-1β]—H-2β—H-3α) was finally elucidated from strong ^{1}H-^{1}H COSY cross signals and has been summarized in Figure 2. It is worth mentioning the strong ^{1}H-^{1}H COSY correlation and the relatively large ^4J constant between H-3α and H-1α signals, a likely consequence of flat zig-zag (W) arrangement in the compound skeleton. This arrangement would not be present if the hydroxyl group were at the 3α position, whereas 1β,3β NOE interaction could be expected. Moreover, as reported, the δ_H 4.40 band width is reduced after shaking with D_2O (at 250 MHz the HO signal overlaps/exchanges with the "water" band at ca. δ_H 1.6).



neoajugapyrin A **(1)**: R_1 = H, R_2 = OH, R_3 = OTig
scutegalerin A **(2)**: R_1 = OH, R_2 = H, R_3 = OTig
scutegalerin B **(3)**: R_1 = R_3 = OH, R_2 = H
scutecolumnin C **(4)**: R_1 = R_2 = H, R_3 = OH
scutecyprin: R_1 = R_2 = H, R_3 = OTig
scupolin G: R_1 = H, R_2 = OH, R_3 = OMePr
14,15-dihydrojodrellin T: R_1 = OTig, R_2 = H, R_3 = OAc

Figure 1: Structures of isolated *neo*- clerodanes and compounds used in the discussion

Table 1: Neoajugapyrin A (**1**)[a] and scutegalerins A (**2**)[b] and B (**3**)[b] NMR data.

position	**1**			**2**			**3**	
	δ ^{13}C, nH	δ ^{1}H	m, *J* (in Hz)	δ ^{13}C, nH	δ ^{1}H	m, *J* (in Hz)	δ ^{1}H	m, *J* (in Hz)
1	22.6, CH_2	2.30	dddd, 14.7; 4.9; 4.0; 2.1	67.1, CH	4.38	ddd[g], 3.9; 3.0; 1.2	4.33	ddd, 4.6; 3.2; 1.1
		1.90	ddd, 14.6; 11.5; 0.9					
2	71.0, CH	3.98	ddd, 4.9; 3.1; 0.8	69.3, CH	4.11	dt, 5.1; 2.7	4.10	dt, 4.9; 2.6
3	70.1, CH	4.40	ddd, 5.1; 2.9; 1.9 (2.1)	30.9, CH_2	2.46	br d, 14.4	2.49	br dd, 14.3; 2.5
					2.25	m[h]	ca. 2.22	m[h]
4	65.9, C			60.1, C				
5	42.5, C			43.4, C				
6	68.2, CH	4.63	dd, 11.9; 4.7	67.8, CH	4.62	dd, 11.7; 4.5	4.68	dd, 11.3; 4.6
7	33.3, CH_2	1.65[e]		32.5, CH_2	1.63	m[h]	ov[i]	-
		1.39	ddd, 13.1; 4.6; 3.0		1.37	ddd, 13.0; 4.5; 2.9	ca. 1.45	m[h]
8	35.4, CH	1.53	dqd 12.8; 6.6; 3.1	35.6, CH	1.53	m[h]	ov[i]	-
9	41.2, C			40.5, C				
10	40.7, CH	1.98	dd, 11.6; 3.9	51.8, CH	1.76	d, 2.9	1.71	d, 3.2
11	86.4, CH	4.09	dd, 11.0; 5.7	87.2, CH	4.09	dd, 11.3;5.0	4.07	dd, 11.8; 5.1
12	33.3, CH_2	1.92[e]		33.6, CH_2	1.97	td, 12.5;9.3	1.97	td, 12.0; 9.4
		1.65[e]			1.65	m[h]	ov[i]	-
13	41.8, CH	2.84	br ddd, 5.1; 3.0; 1.2	41.6, CH	2.92	br tt[f], 9.2; 4.6	2.92	br tt[f], 9.4; 4.7
14	32.6, CH_2	2.15	ddt, 12.7; 9.2; 8.3	32.7, CH_2	2.22	m[h]	ca. 2.22	m[h]
		1.72[e]			1.74	m[h]	ca. 1.74	m[h]
15B[c]	68.3, CH_2	3.8765	ddd, 8.8; 8.7; 6.6	68.9, CH_2	3.9414	ddd, 8.8; 8.2; 6.7	3.94	-
15A[c]		3.8617	ddd, 8.7; 8.1; 4.5		3.8755	ddd, 8.8; 7.9; 4.5	3.88	-
16	108.1, CH	5.63	d, 5.1	108.4, CH	5.69	d, 5.2	5.69	d, 5.2
17	16.4, CH_3	0.89	d, 6.1	16.0, CH_3	0.89	d, 6.6	0.90	d, 6.3
18B[d]	44.1, CH_2	3.09	d, 4.3	50.4, CH_2	3.00	d, 4.3	2.96	d, 4.0
18A		2.88	d, 4.3		2.51	d, 4.3	2.51	d, 4.0
19	91.0, CH	6.76	s	90.5, CH	6.68	s	5.61	s
20	14.3, CH_3	1.19	s	16.3, CH_3	1.22	s	1.16	s
1' (C=O)	166.0, C			166.4, C				
2'	128.7, C			128.8, C				
3'	138.7, CH	7.06	qq, 7.1; 1.4	138.7, CH	7.11	qq, 7.0; 1.5		
4'	14.5, CH_3	1.80	dq, 7.1; 1.2	14.6, CH_3	1.81	dq, 7.1; 1.1		
5'	11.9, CH_3	1.87	quint[f], 1.3	11.9, CH_3	1.90	dq[f], 1.2		
6[1] (C=O)	170.0, C			169.9, C				
6[2] (Me)	21.0, CH_3			21.0, CH_3	1.80	s	2.06	s
(HO)		2.05	d, 5.3		3.51			
(HO)		2.39						

[a] $CDCl_3$, ^{1}H 600.13 MHz, δ_{ref} 7.26; ^{13}C 150.9 MHz, δ_{ref} 77.0 ppm; [b] $CDCl_3$, ^{1}H 400 MHz, δ_{ref} 7.26; ^{13}C 101 MHz, δ_{ref} 77.0 ppm; [c] δ ^{1}H adjusted by spin simulation; [d] endo hydrogen; [e] data from COSY; [f] apparent multiplicity; [g] after D_2O addition; [h] multiplicity and coupling constants could not be estimated; [i] overlapped with the "water" band at ca. δ_H 1.6.

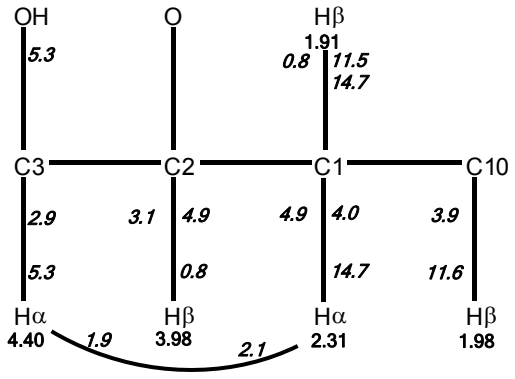


Figure 2: Ring A spin system of **1** (H-10—[H-1α–H-1β]—H-2β—H-3α; *J* in ***italics***)

Therefore, the structure was elucidated as 3β-hydroxyscutecyprin (and named as neoajugapyrin A to indicate the change to a new revised structure supported by NMR data, as discussed). Additional inferences could be drawn by comparison of selected NMR spectral data for H-1α and H-3α in neoajugapyrin A with those of some *neo*-clerodanes with 2α,19 and 4α,18 epoxy rings [4,5,12,14], as given in Table 2. As a whole, the ^{1}H NMR spectrum of **1** is very close to that of scutecyprin and scupolin G and similar to that of 14,15-dihydrojodrellin T.

Table 2: C-1/C-3 substitution effects in *neo*-clerodanes with 2α,19 and 4α,18 epoxy rings.

compound	substitution		δ_H	δ_H	δ_C
	C-1	C-3	H-1α	H-2β/H-3α	C-4/C-18
neoajugapyrin A, **1**	H_2	H,OH	2.31 dddd	3.98 ddd 4.9,3.1,0.8/ 4.40 ddd 5.3,2.9,1.9	65.9/44.1
scupolin G	H_2	H,OH	n.r.[a]	4.32 m w½ 4.5/ 3.95 dd 4.1,3.2[b]	65.8/44.0[b]
scutecyprin	H_2	H_2	n.r.[a]	4.18 m w½ 6/ 2.55 br d 14.3[c]	60.6/50.2[c]
			2.36 dtd[d]	4.18 dt 4.4,2.8/ 2.55 dt 14.3,2.8[d]	60.6/50.2[d]
14,15-dihydrojodrellin T	H,OTig	H_2	5.51 m[e]	4.42 dt 5.3,2.6/ 2.48 br d14.8[e]	59.6/50.2[f]

[a] data not reported; [b] data from [14]; [c] data from [12]; [d] Bozov PI, Penchev PN, unpublished NMR spectral data; [e] data from [4]; [f] data from [5].

As can be seen, the reported H-2β/H-3α assignment for scupolin G [14] may also be reversed (the rational for the irradiation result changes $^{4}J_{H\text{-}3,H\text{-}1}$ to $^{3}J_{H\text{-}2,H\text{-}1}$. = 3.2 Hz). Therefore, the HO-substitution effect must be an up-field rather than downfield shift at the vicinal proton: $\delta_{H\text{-}2\beta}$ 4.18 (in scutecyprin) to 3.95 instead of to 4.32 (in scupolin G). From Table 2, the δ_H for H-1α are very close in neoajugapyrin A and scutecyprin, as well as the δ_H for H-2β/H-3α in neoajugapyrin A/scupolin G and scutecyprin/14,15-dihydrojodrellin T, thus reflecting the methylene group at the corresponding position. Also, the hydroxyl group at C-3 (as in neoajugapyrin A and scupolin G) leads to either a high- or low-frequency shift of about 5-6 ppm for C-4 or C-18 carbon signals (last column of Table 2).

To our surprise, spectral data for **2** pointed to the true 1β-hydroxy-scutecyprin structure. Again, two H-C-O signals were part of ring A, but now, one was located at δ_H 4.38 and coupled to a δ_H 1.77 doublet (J = 2.9 Hz), pointing out the HC(1)-HC(10) relationship. Furthermore, this presumed HC(1)-O signal was coupled to the second H-C-O multiplet (δ_H 4.11, dqcosy) partly overlapping with HC(11)-O (δ_H 4.09). The four cross peaks displayed at δ_H 4.09/4.11 (δ_H 2.44, 2.22, 1.97 and 1.65) were sorted out as each pair in the HSQC spectrum by correlation with δ_C 30.8 (the first two) and δ_C 33.5 (the last two). Therefore, they could be assigned as C-3 and C-12, respectively. Thus, after a detailed study of the multiplicities, the spin system of ring A could be completed as shown in Figure 3.

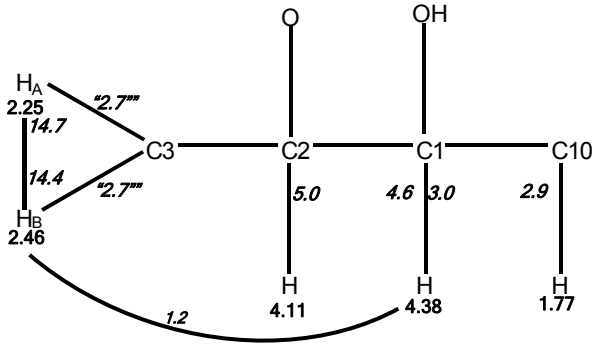


Figure 3: Ring A spin system of **2** (H-10—H-1α—H-2β—[H-3A–H-3B]; *J* in ***italics***).

Further evidence supporting the stereochemistry was derived from NOESY results: H-C(6) interaction with H_B-C(18), H-C(8) and H-C(10) places all of them on the same β-side, and H-C(1) with H-C(20) on the same α-side. The pattern recognition (both as ddd) of the $H_2C(15)$ spin subsystem (AB part of an AB-XY-M-xy-a spin system) is worthy of mention, owing to the anisotropic effect upon hydroxyl substitution at C-1. Chemical shifts and coupling constants reported in Table 1 were adjusted by spin simulation (and in turn those of **1**). The now isolated 1β-hydroxyscutecyprin was named scutegalerin A (**2**).

A third (minor) isolated compound displayed most of the ^{1}H NMR structural features as **2** (Table 1). However, the tigloyl substituent signals were not present, while the expected change for a hydroxyl group as a C-19 substituent was observed [HC(19): δ_H 5.61 vs. δ_H 6.68 ppm). The compound (1β-hydroxyscutecolumnin C) was named scutegalerin B (**3**).

Scutecolumnin C (**4**) was identified (based on ^{1}H NMR data) as the fourth isolated *neo*-clerodane and is reported for the first time in this species. It has been found previously in extracts of *S. columnae* [15,16], *S. alpina* [17] and *S. alpina* subsp. *javalambrensis* [18].

Experimental

Structural data: ^{1}H NMR spectra were recorded on either Bruker DRX-250, Varian Mercury-400 or Bruker Avance II+ spectrometers, operating at 250.13 MHz, 400.13 or 600.130 MHz, respectively. ^{13}C NMR spectra were recorded at 100.61 and 150.903 MHz, respectively on the corresponding spectrometers. TMS was used as internal standard and $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in ppm and coupling constants (J) in Hertz. The IR spectra of **1** and **4** were registered in KBr pellets on a Perkin-Elmer 1750 FT-IR spectrometer from 4000 cm^{-1} to 450 cm^{-1} at resolution 4 cm^{-1} with 9 scans.

Plant material: The stems of *Scutellaria galericulata* were collected in June 2012 near Pleven, Bulgaria, and voucher specimens (no. 11927) were deposited in the Herbarium of the Higher Institute of Agriculture at Plovdiv, Bulgaria.

Extraction and isolation: Dried and finely powdered aerial parts of *S. galericulata* (2.8 kg) were extracted with Me_2CO (3 x 8 L) at room temperature for a week. After filtration, the solvent was evaporated to dryness under reduced pressure and low temperature (<40°C) yielding a gum (35.2 g), which was dissolved in aq. Me_2CO (40% H_2O, v/v, 100 mL). This solution was cooled to 4°C for 24 h and filtered. The filtrate was extracted with $CHCl_3$ (3 x 200 mL) and the organic layer was dried (Na_2SO_4) and evaporated in vacuum to afford a residue (3.9 g, bitter fraction). This was subjected to CC (45 g silica gel Merck n. 7734, deactivated with 10% H_2O, w/w). Pure light petroleum (5 L), followed by a gradient of light petroleum - EtOAc mixtures (10:1 to 4:1) and dichloromethane were used first as eluting solvents. The diterpene fractions (100 mL each) were eluted with 2% methanol in DCM yielding scutecolumnin C (**4**, 6 mg, 3 flasks) followed by 39.5 mg of a mixture (4 flasks, two TLC spots upon EtOAc elution) and 53 mg of **1** (10 flasks). Repeated prep TLC of the mixture (2% methanol in DCM) afforded further amounts of **4** (1.3 + 2.3 mg) and 19.9 mg of a diterpene mixture. Prep TLC separation of this mixture (*n*-hexane-EtOAc, 1:4, x 3) further yielded **2** (1.6 mg), **3** (0.9 mg) and a minor amount of **4**.

Neoajugapyrin A (1)
Colorless needles from acetone.
MP: 200-202°C (lit. [11] MP: 198-200° from Et_2O-petrol).
TLC: R_f 0.67 (EtOAc).
IR (KBr): 3403, 2967, 2939, 2901, 2873, 1723, 1698, 1654, 1464, 1386, 1336, 1295, 1261, 1250, 1158, 1092, 1082, 1066, 1052, 1018, 986, 966, 942, 918, 899, 875, 835, 777, 732, 679, 628, 603, 568, 527, 485, 469 cm^{-1}.
^{1}H and ^{13}C NMR: Table 1 (Supplementary data Table 1A).
calcd for $C_{27}H_{38}O_9$: 506.251585 (lit. [11]: *m/z* (rel. int.) 506 $[M]^+$ (0.12); $C_{17}H_{38}O_4$ (wrong formula) requires: C, 64.01, H 7.56%; Found: C, 62.19; H, 7.41)

Scutegalerin A (2)
Colorless oil
TLC: R_f 0.49 (EtOAc)
^{1}H and ^{13}C NMR: Table 1 (Supplementary data Table 1B).

Scutegalerin B (3)
Colorless oil
TLC: R_f 0.49 (EtOAc).
^{1}H NMR: Table 1.

Scutecolumnin C (4)
TLC: R_f 0.81 (EtOAc).
IR (KBr): 3444, 2960, 2877, 1729, 1648, 1456, 1374, 1249, 1093, 1021, 970, 921, 878, 732, 601 cm^{-1}.
^{1}H and ^{13}C NMR: as in [17] with minor differences

Supplementary data: Tables of complete spectral data and the ^{1}H NMR, ^{13}C NMR and 2D NMR spectra (with enlarged detailed sections for multiplets and cross peaks) are included in a "Supplementary Data" section.

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References

[1] Bruno M, Piozzi F, Rosselli S. (**2002**) Natural and hemisynthetic neoclerodane diterpenoids from *Scutellaria* and their antifeedant activity. *Natural Product Reports*, ***19***, 357-378.

[2] Anderson JC, Blaney WM, Cole MD, Fellows LL, Ley SV, Sheppard RN, Simmonds MSJ. (**1989**) The structure of two new clerodane diterpenoid potent insect antifeedants from *Scutellaria woronowii* (Juz); jodrellin A & B. *Tetrahedron Letters*, ***30***, 4737-4740.

[3] Cole MD, Bridge PD, Dellar JE, Fellows LE, Clare Cornish M, Anderson JC. (**1991**) Antifungal activity of *neo*-clerodane diterpenoids from *Scutellaria. Phytochemistry*, ***30***, 1125-1127.

[4] Cole MD, Anderson JC, Blaney WM, Fellows LE, Ley SV, Sheppard RN, Simmonds MSJ. (**1990**) Neo-clerodane insect antifeedants from *Scutellaria galericulata. Phytochemistry*, ***29***, 1793-1796.

[5] Rodríguez B, de la Torre MC, Rodríguez B, Bruno M, Piozzi F, Savona G, Simmonds MSJ, Blaney WM, Perales A. (**1993**) *neo*-Clerodane insect antifeedants from *Scutellaria galericulata. Phytochemistry*, ***33***, 309-315.

[6] Rodríguez B, de la Torre MC, Rodríguez B, Gómez-Serranillos P. (**1996**) *neo*-Clerodane diterpenoids from *Scutellaria galericulata. Phytochemistry*, ***41***, 247-253.

[7] Boneva IM, Malakov PY, Papanov GY, Tomova K. (**1999**) Diterpenoids and sterols from *Scutellaria galericulata. Bulgarian Chemical Communications*, ***31***, 269-275.

[8] Bozov PI, Malakov PY, Papanov GY, de la Torre MC, Rodríguez B, Perales A. (**1993**) Scutalpin A, a *neo*-clerodane diterpene from *Scutellaria alpina. Phytochemistry*, ***34***, 453-456.

[9] Bozov PI, Papanov GY, Malakov PY. (**1994**) *neo*-Clerodane diterpenoids from *Scutellaria alpina. Phytochemistry*, ***35***, 1285-1288.

[10] Malakov PY, Bozov PI, Papanov GY. (**1997**) A neo-clerodane diterpenoid from *Scutellaria orientalis* subs. *pinnatifida. Phytochemistry*, ***46***, 587-589.

[11] Boneva IM, Malakov PY, Papanov GY. (**1998**) Ajugapyrin A, a *neo*-clerodane diterpene from *Ajuga pyramidalis*. *Phytochemistry*, ***47***, 303-305.

[12] Bruno M, de la Torre MC, Piozzi F, Rodríguez B, Savona G, Arnold NA. (**1993**) A neo-clerodane diterpenoid from *Scutellaria cypria* var. *elatior. Phytochemistry*, ***33***, 931-932.

[13] Fraser RR. (**1960***)* Long-range coupling constants in the NMR spectra of olefins. *Canadian Journal of Chemistry*, ***38***, 549-553.

[14] de la Torre MC, Rodríguez B, Bruno M, Vassallo N, Bondi ML, Piozzi F, Servettaz O. (**1997**) Neoclerodane diterpenoids from *Scutellaria polyodon*. *Journal of Natural Products*, ***60***, 1229-1235.

[15] de la Torre MC, Bruno M, Piozzi F, Rodríguez B, Savona G, Servettaz O. (**1992**) *neo*-Clerodane diterpenoids from *Scutellaria columnae*. *Phytochemistry*, ***31***, 3639-3641.

[16] Malakov PY, Papanov GY, Deltchev VB. (**1998**) 1l-Episcutecolumnin C, a *neo*-clerodane diterpenoid from *Scutellaria columnae. Phytochemistry*, ***49***, 811-815.

[17] de la Torre MC, Rodríguez B, Bruno M, Piozzi F, Savona G, Vassallo N, Servettaz O. (**1995**) *neo*-Clerodane diterpenoids from *Scutellaria alpina. Phytochemistry*, ***38***, 181-187.

[18] Muñoz DM, de la Torre MC, Rodríguez B, Simmonds MSJ, Blaney WM. (**1997**) Neo-clerodane insect antifeedants from *Scutellaria alpina* subsp. *javalambrensis. Phytochemistry*, ***44***, 593-597.